CHAPTER 8
Jaundice

KEY TEACHING POINTS

- Bedside examination is accurate in four settings: diagnosing the etiology of jaundice (i.e., hepatocellular disease versus obstructed biliary ducts), recognizing cirrhosis, diagnosing hepatopulmonary syndrome, and diagnosing portopulmonary hypertension.
- In patients with jaundice, dilated abdominal veins, palmar erythema, spider angiomas, and ascites all increase the probability of hepatocellular disease. A palpable gallbladder increases the probability of extrahepatic obstruction.
- In patients with chronic liver disease, dilated abdominal veins, asterixis, reduced body hair, gynecomastia, ascites, spider angiomas, jaundice, palmar erythema, and a firm liver edge all increase the probability of cirrhosis.
- In patients with cirrhosis, clubbing and cyanosis increase the probability of hepatopulmonary syndrome.
- In patients with cirrhosis, a loud P2, right ventricular heave, and blood pressure of 140/90 or more increase the probability of portopulmonary hypertension.

I. INTRODUCTION

Jaundice is an abnormal yellowish discoloration of the skin and mucous membranes caused by accumulation of bile pigment. There are three forms: (1) hemolytic jaundice (due to increased bilirubin production from excessive breakdown of red cells), (2) hepatocellular jaundice (due to disease of the liver parenchyma, e.g., alcoholic liver disease, drug-induced liver disease, viral hepatitis, or metastatic carcinoma), and (3) obstructive jaundice (due to mechanical obstruction of the biliary ducts outside the liver, e.g., choledocholithiasis or pancreatic carcinoma). In most published series of jaundiced patients, hemolysis is uncommon, and the usual task of the clinician at the bedside is to distinguish hepatocellular disease from obstructed biliary ducts.[1,2]

II. THE FINDINGS

A. JAUNDICE

Jaundice is usually first noted in the eyes, but the traditional term for this finding (scleral icterus) is actually a misnomer because pathologic studies reveal most of the pigment to be deposited in the conjunctiva, not the avascular sclera.[3] As jaundice progresses and the serum bilirubin increases, the face, mucous membranes, and eventually the entire skin acquire a yellow or orange hue.

Prominent yellowish subconjunctival fat may be mistaken for conjunctival jaundice, but fat is usually limited to the conjunctival folds and, unlike jaundice, spares the area near the cornea. Patients with carotenemia (from excess carrot or multivitamin ingestion) also develop a yellowish discoloration of the skin, especially the palms, soles, and nasolabial fold, but in contrast to jaundice, the conjunctiva are spared.[4]

B. ASSOCIATED FINDINGS

According to classic teachings, several findings distinguish hepatocellular disease from obstructed biliary ducts.

1. HEPATOCELLULAR JAUNDICE

Characteristic findings are spider telangiectasia, palmar erythema, gynecomastia, dilated abdominal wall veins, splenomegaly, asterixis, and fetor hepaticus.

A. SPIDER TELANGIECTASIA (SPIDER ANGIOMAS)

Spider telangiectasia are dilated cutaneous blood vessels with three components: (1) a central arteriole (the "body" of the spider) that can be seen to pulsate when compressed slightly with a glass slide; (2) multiple radiating "legs"; and (3) surrounding erythema, which may encompass the entire lesion or only its central portion.[5] After blanching, the returning blood fills the central arteriole first before traveling to the peripheral tips of each leg. Spiders are most numerous on the face and neck, followed by the shoulders, thorax, arms, and hands. They are rare on the palms, scalp, and below the umbilicus. This peculiar distribution may reflect the neurohormonal properties of the microcirculation, because it is similar to the distribution of where blushing is most intense.[5]

Acquired vascular spiders are associated with three clinical conditions: liver disease, pregnancy, and malnutrition.[6] In patients with liver disease, the spiders advance and regress with disease severity,[7] and their appearance correlates somewhat with an abnormally increased ratio of serum estradiol to testosterone levels.[8] In pregnant women, spiders typically appear between the second and fifth months and usually disappear within days after delivery.[6] Vascular spiders also have been described in normal persons, but these lesions, in contrast to those of liver disease, are always small in number (with an average of three) and size.[5]

Vascular spiders were first described by the English physician Erasmus Wilson in 1867.[5]

B. PALMAR ERYTHEMA

Palmar erythema is a symmetric reddening of the surfaces of the palms, most pronounced over the hypothenar and thenar eminences.[6] Palmar erythema occurs in the same clinical conditions as vascular spiders, and the two lesions tend to come and go together.[6]

C. GYNECOMASTIA AND DIMINISHED BODY HAIR

Many patients with liver disease have gynecomastia (defined as a palpable, discrete button of firm subareolar breast tissue 2 or more cm in diameter) and diminished pubic and body hair, both findings attributed to increased circulating estrogen-to-testosterone levels.

D. DILATED ABDOMINAL VEINS

In some patients with cirrhosis, elevated portal venous pressures lead to the development of collateral vessels from the portal venous to systemic venous

systems. One group of such vessels surrounds the umbilicus, decompressing the left portal vein via paraumbilical vessels into abdominal wall veins.[9] Sometimes these abdominal wall veins become so conspicuous they resemble a cluster of serpents, thus explaining their common label **caput medusae**.[10] Collateral vessels may generate a continuous humming murmur heard during auscultation between the xiphoid and umbilicus.[11]

Collateral abdominal vessels also may appear in patients with the superior vena cava syndrome (if the obstruction also involves the azygous system)[12] or inferior vena cava syndrome.[13] In these disorders, however, the vessels tend to appear on the lateral abdominal wall. A traditional test to distinguish inferior vena cava obstruction from portal hypertension is to strip abdominal wall veins below the umbilicus and see which way blood is flowing. (In portal-systemic collaterals, blood should flow away from the umbilicus toward the patient's feet, whereas in inferior vena cava collaterals, flow is reversed toward the head.) Even so, this test is unreliable because most dilated abdominal vessels lack competent valves, and the clinician can "demonstrate" blood to flow in either direction in most patients with both conditions.

E. PALPABLE SPLEEN

One of the principal causes of splenomegaly is portal hypertension from severe hepatocellular disease.[14] Therefore, a traditional teaching is that the finding of splenomegaly in a jaundiced patient increases the probability of hepatocellular disease.

F. ASTERIXIS

Originally described by Adams and Foley in 1949,[15,16] asterixis is one of the earliest findings of hepatic encephalopathy and is thus a finding typical of hepatocellular jaundice. To elicit the sign, the patient holds both arms outstretched with fingers spread apart. After a short latent period, both fingers and hands commence to "flap," with abrupt movements occurring at irregular intervals of a fraction of a second to seconds (thus earning the name *liver flap*). The fundamental problem in asterixis is the inability to maintain a fixed posture (the word *asterixis* comes from the Greek *sterigma*, meaning "to support"), and consequently asterixis can also be demonstrated by having the patient elevate the leg and dorsiflex the foot, close the eyelids forcibly, or protrude the tongue.[15] Because some voluntary contraction of the muscles is necessary to elicit asterixis, the sign disappears once coma ensues (although some comatose patients exhibit the finding during the grasp reflex; see Chapter 63).[15]

Electromyography reveals that asterixis represents the abrupt disappearance of electrical activity in the muscle (i.e., negative myoclonus).[17] Asterixis is not specific to liver disease but also appears in encephalopathy from other causes, such as hypercapnia or uremia.[18] Unilateral asterixis indicates structural disease in the contralateral brain.[19,20]

G. FETOR HEPATICUS

Fetor hepaticus is the characteristic breath of patients with severe hepatic parenchymal disease, an odor likened to a mixture of rotten eggs and garlic. Gas chromatography reveals that the principal compound causing the odor is dimethylsulfide.[21] Fetor hepaticus correlates best with severe portal-systemic shunting, not encephalopathy per se, because even alert patients with severe portal-systemic shunting have the characteristic breath.[22]

2. OBSTRUCTIVE JAUNDICE: PALPABLE GALLBLADDER (COURVOISIER SIGN)

The presence of a smooth, nontender, distended gallbladder in a patient with jaundice is a traditional sign of obstructive jaundice. Courvoisier sign refers to the association of the palpable gallbladder and extrahepatic obstruction, a sign discussed fully in Chapter 51.

III. CLINICAL SIGNIFICANCE

A. DETECTION OF JAUNDICE

Although many textbooks claim jaundice becomes evident once the serum bilirubin exceeds 2.5 to 3 mg/dL, clinical studies reveal that only 70% to 80% of observers detect jaundice at this threshold.[23,24] The sensitivity of examination increases to 83% when bilirubin exceeds 10 mg/dL and 96% when it exceeds 15 mg/dL.

B. HEPATOCELLULAR VERSUS OBSTRUCTIVE JAUNDICE

Studies show that clinicians accurately distinguish hepatocellular from obstructive jaundice more than 80% of the time by just using bedside and basic laboratory findings (i.e., before clinical imaging).[25,26] In EBM Box 8.1, *disease* is arbitrarily defined as hepatocellular disease: therefore, likelihood ratios (LRs) with large positive values *increase* the probability of hepatocellular disease, whereas those with values close to zero decrease it and thus *increase* probability for obstructive disease.

These studies show that in patients presenting with jaundice, the physical signs of portal hypertension (dilated abdominal veins, LR = 17.5; ascites, LR = 4.4; and palpable spleen, LR = 2.9), palmar erythema (LR = 9.8), and spider angiomas (LR = 4.7) all increase the probability of hepatocellular jaundice. The only finding arguing strongly *against* hepatocellular jaundice is the palpable gallbladder (LR = 0.04; in other words, the finding of a palpable gallbladder argues *for* obstructed bile ducts with an LR of 26, the inverse of 0.04).

Weight loss does not help discriminate between hepatocellular and obstructive etiologies. Other unhelpful signs are liver tenderness and a palpable liver. The palpable liver remains unhelpful even when defined as a liver edge extending more than four to five fingerbreadths below the right costal margin.[25]

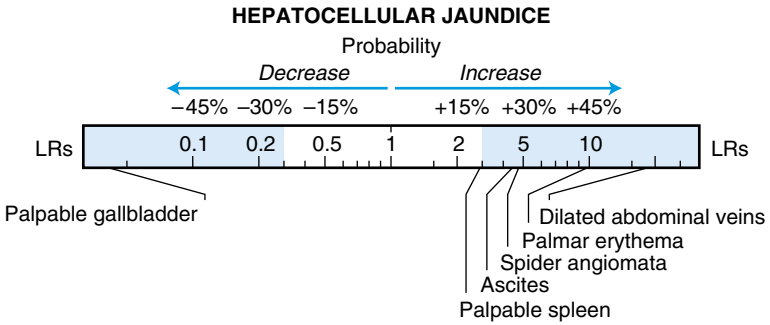
C. DIAGNOSIS OF CIRRHOSIS

The diagnosis of cirrhosis in patients with liver disease has important prognostic and therapeutic implications. EBM Box 8.2 displays the diagnostic accuracy of physical findings in detecting cirrhosis, determined from hundreds of patients presenting with diverse chronic liver diseases. According to this EBM Box, the findings increasing the probability of cirrhosis the most are dilated abdominal wall veins (LR = 9.5), encephalopathy (irrational behavior, disordered consciousness, or asterixis; LR = 8.8), reduced body or pubic hair (LR = 8.8), gynecomastia (LR = 7), ascites (LR = 6.6), spider angiomas (LR = 4.2), jaundice (LR = 3.8), palmar erythema (LR = 3.7), a liver edge that is firm to palpation (LR = 3.3), and peripheral edema (LR = 3). Other helpful findings (though less compelling ones) are a palpable liver in the epigastrium (LR = 2.7) and splenomegaly (LR = 2.5). The only findings decreasing the probability of cirrhosis in these patients are the *absence* of a palpable liver in the epigastrium (LR = 0.3) and the *absence* of a firm liver edge (LR = 0.4).

EBM BOX 8.1
*Diagnosing Hepatocellular Disease in Patients With Jaundice**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
General Appearance				
Weight loss[25,27]	10-49	21-97	NS	NS
Skin				
Spider angiomas[25,27]	35-47	88-97	**4.7**	0.6
Palmar erythema[25]	49	95	**9.8**	0.5
Dilated abdominal veins[25]	42	98	**17.5**	0.6
Abdomen				
Ascites[25]	44	90	**4.4**	0.6
Palpable spleen[25,27]	29-47	83-90	2.9	0.7
Palpable gallbladder[25]	0†	69	**0.04**	1.4
Palpable liver[25,27]	71-83	15-17	NS	NS
Liver tenderness[25,27]	37-38	70-78	NS	NS

*Diagnostic standard: for *nonobstructive* (*vs. obstructive*) *jaundice*, needle biopsy of liver, surgical exploration, or autopsy.
†None of the 41 patients with medical jaundice in this study had a palpable gallbladder; for calculation of the LRs, 0.5 was added to all cells of the 2 × 2 table.
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
Click here to access calculator



EBM BOX 8.2
*Diagnosing Cirrhosis in Patients With Chronic Liver Disease**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
Skin				
Spider angiomas[28-39]	33-84	48-98	**4.2**	0.5
Palmar erythema[29,31,32,34,37,39]	12-70	49-98	**3.7**	0.6
Gynecomastia[29,37]	18-58	92-97	**7.0**	NS
Reduction of body or pubic hair[29,37]	24-51	94-97	**8.8**	NS
Jaundice[29,33,35,37,40]	16-44	83-99	**3.8**	0.8
Dilated abdominal wall veins[29,34,37]	9-51	79-100	**9.5**	NS
Abdomen				
Hepatomegaly[29,32-36,38,41]	31-96	20-96	2.3	0.6
Palpable liver in epigastrium[35,38]	50-86	68-88	2.7	**0.3**
Liver edge firm to palpation[32,39,41]	71-78	71-90	**3.3**	0.4
Splenomegaly[28,30-36,38,40,41]	5-85	35-100	2.5	0.8
Ascites[28,29,31,33-35,40]	14-52	82-99	**6.6**	0.8
Other				
Peripheral edema[29,33,34]	24-56	87-92	**3.0**	0.7
Encephalopathy[28,29,31]	9-29	98-99	**8.8**	NS

*Diagnostic standard: For *cirrhosis*, needle biopsy of liver.
†Definition of findings: For *hepatomegaly* and *splenomegaly*, examining clinician's impression using palpation, percussion, or both; for *encephalopathy*, disordered consciousness and asterixis.[15]
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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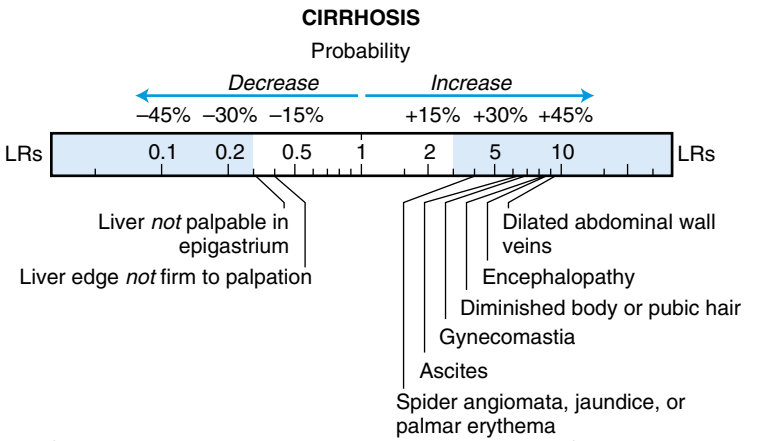

D. DETECTING LARGE GASTROESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS

In studies of more than 750 patients with cirrhosis who have not had prior gastrointestinal bleeding, no physical finding reliably predicts which patients have significant gastroesophageal varices (as detected by endoscopy). For all findings—caput medusae, spider angiomas, jaundice, hepatomegaly, splenomegaly, or hepatic encephalopathy—the LRs are 1.5 or less or not significant.[42-46]

E. DETECTING HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome is a serious complication of cirrhosis, causing intrapulmonary vascular shunting and significant hypoxemia. In eight studies of over 550 patients with cirrhosis, most of them awaiting liver transplantation, the findings of finger clubbing (LR = 4) and cyanosis (LR = 3.6) increased the probability of hepatopulmonary syndrome (EBM Box 8.3). The Child prognostic score (for chronic liver disease)* is also useful: Child class C increases the probability of hepatopulmonary syndrome (LR = 3.1), whereas Child class A or B decreases it (LR = 0.4).[51,52]

F. DETECTING PORTOPULMONARY HYPERTENSION

Some patients with end-stage liver disease develop pulmonary hypertension, a significant complication because it greatly increases the surgical risk of liver transplantation. In one study of 80 consecutive liver transplant candidates, three physical findings accurately detected pulmonary hypertension (mean pulmonary artery pressure of 25 mm Hg or higher): a loud P2 (pulmonary component of the second heart sound, EBM Box 8.3; LR = 17.6), right ventricular heave (LR = 8.8), and systemic hypertension (blood pressure 140/90 or higher, LR = 7.3).[54] At first glance, the association between systemic and pulmonary hypertension may be unexpected, but most patients with end-stage liver disease actually have a normal or low blood pressure from systemic vasodilation, suggesting that the association between pulmonary and systemic hypertension represents a generalized abnormality of vascular tone.

The presence of oxygen desaturation, elevated neck veins, ascites, and edema does not affect the probability of pulmonary hypertension in these patients (EBM Box 8.4).

The references for this chapter can be found on www.expertconsult.com.

* The Child score (or Child-Pugh score) predicts the prognosis of patients with chronic liver disease by addressing five clinical variables (bilirubin, albumin, prothrombin time, ascites, and hepatic encephalopathy) and scoring each 1 to 3 based on levels of abnormality. The combined score distinguishes Child classes A (best prognosis), B, and C (worst prognosis).

EBM BOX 8.3

*Diagnosing Hepatopulmonary Syndrome in Patients With Chronic Liver Disease**

Finding (Reference)	*Sensitivity (%)*	*Specificity (%)*	**Likelihood Ratio† if Finding Is**	
			Present	*Absent*
Clubbing[47-52]	22-80	64-95	**4.0**	0.5
Cyanosis[47,48,52]	8-86	78-99	**3.6**	NS
Palmar erythema[47,53]	57-80	54-70	NS	NS
Spider angioma[47-53]	39-97	26-87	1.6	0.5
Ascites[49-51]	55-94	20-57	NS	NS

*Diagnostic standard: For *hepatopulmonary syndrome,* all three of the following criteria were present: (1) cirrhosis, (2) contrast echocardiography revealing intrapulmonary right → shunting, and (3) hypoxemia, variably defined as arterial pO_2 <70 mm Hg,[53] or <80 mm Hg,[47,51] alveolar-arterial pO_2 gradient ≥15 mm Hg[50,52] or >20 mm Hg,[48] or *either* pO_2 <70 mm Hg or $AapO_2$ >20 mm Hg.[49]

†Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.

NS, Not significant.

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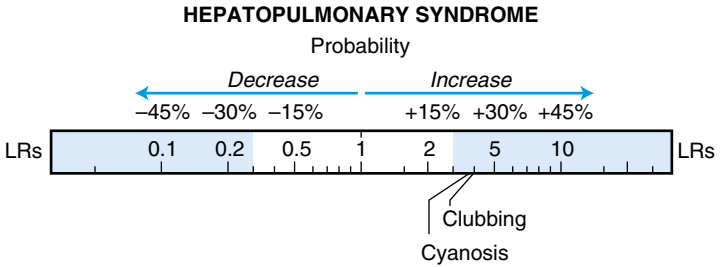

EBM BOX 8.4

*Diagnosing Pulmonary Hypertension in Patients With Cirrhosis**

Finding[54]	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio† if Finding Is	
			Present	*Absent*
Vital Signs				
Blood pressure ≥140/90	63	91	**7.3**	NS
Oxygen saturation <92%	25	89	NS	NS
Heart Examination				
Elevated neck veins	13	94	NS	NS
Right ventricular heave	38	96	**8.8**	NS
Loud P2	38	98	**17.6**	NS
Other				
Ascites, edema, or both	75	36	NS	NS

*Diagnostic standard: For *pulmonary hypertension*, measured mean pulmonary artery pressure ≥25 mm Hg.
†Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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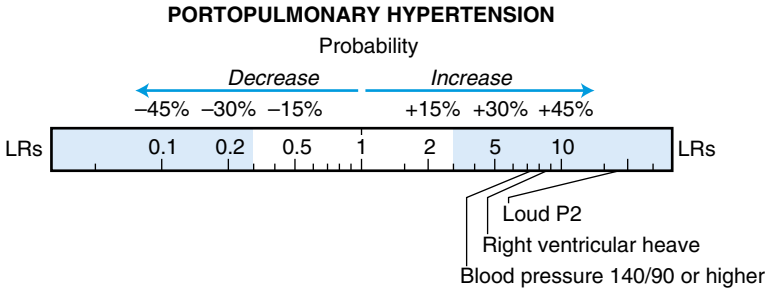

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